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Glutamate receptor antagonists for tinnitus (Protocol)

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[Intervention Protocol]

Glutamate receptor antagonists for tinnitus

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To evaluate the effects and safety of glutamate receptor antagonist medications prescribed for tinnitus.

BACKGROUND

The following paragraphs and Description of the condition are based on the Cochrane Review 'Amplification with hearing aids for patients with tinnitus and co-existing hearing loss' and reproduced with permission (Hoare 2014).

Tinnitus is defined as the perception of sound in the absence of an external source (Jastreboff 2004). It is typically described by those who experience it as a ringing, hissing, buzzing or whooshing sound and is thought to result from abnormal neural activity at some point or points in the auditory pathway, which is erroneously interpreted by the brain as sound. Tinnitus can be either objective or subjective. Objective tinnitus refers to the perception of sound that can also be heard by the examiner and is usually due to blood flow or muscle movement (Eggermont 2010). Most commonly, however, tinnitus is subjective; the sound is only heard by the person experiencing it and no source of the sound is identified (Jastreboff 1988). Subjective tinnitus affects 10% of the general population, increasing to as many as 30% of adults over the age of 50 years (Davis 2000; Møller 2000). It can be experienced acutely, recovering spontaneously within minutes to weeks, but is considered chronic and unlikely to resolve spontaneously when experienced for six months or more (Hahn 2008; Rief 2005). In England alone there are an estimated ¾ million GP consultations every year where the primary complaint is tinnitus (El-Shunnar 2011), equating to a major burden on healthcare services. For many people tinnitus is persistent and troublesome, and has disabling effects such as insomnia, difficulty concentrating, difficulties in communication and social interaction, and negative emotional responses such as anxiety and depression (Andersson 2009; Crönlein 2007; Marciano 2003). In approximately 90% of cases, chronic tinnitus is co-morbid with some degree of hearing loss, which may confound these disabling effects (Fowler 1944; Sanchez 2002). An important implication in clinical research therefore is that outcome measures of benefit need to distinguish benefits specific to improved hearing from those specific to tinnitus.

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Description of the condition

Diagnosis and clinical management of tinnitus

There is no standard procedure for the diagnosis or management of tinnitus. There are, however, recent guidelines for doing so from the UK Department of Health (Department of Health 2009) and the international organisation, the Tinnitus Research Initiative (Biesinger 2011). Both guidelines recommend that tinnitus and its impact on the person are assessed using validated questionnaire measures of severity, quality of life, depression or anxiety. Psychoacoustic measures of tinnitus (pitch, loudness, minimum masking level) are also recommended. Although these do not correlate well with tinnitus severity (Hiller 2006), they can prove useful in patient counselling (Henry 2004), or to demonstrate stability of the tinnitus percept over time (Department of Health 2009). Recommended clinical management strategies include directive counselling, relaxation therapy, tinnitus retraining therapy (TRT), cognitive behavioural therapy (CBT), sound enrichment using ear-level sound generators or hearing aids, and drug therapies to manage co-morbid symptoms such as insomnia, anxiety or depression (Department of Health 2009). All show variable efficacy and have little known risk of adverse effects (Hoare 2011; Hobson 2010; Martinez-Devesa 2010; Phillips 2010). Where there is a hearing loss and tinnitus, the most common recommendation is to fit a hearing aid, although this practice also varies according to clinical experience and anecdotal evidence. For example, there is a clearly divided opinion among clinicians as to whether or not a hearing aid should be recommended to someone with a mild or higher-frequency hearing loss that ordinarily might go unaided (Hoare 2012).

Pathophysiology

Most people with chronic tinnitus have some degree of hearing loss (Ratnayake 2009), and the prevalence of tinnitus increases with increased hearing loss (Han 2009; Martines 2010). The varying theories of tinnitus generation involve either changes in function or activity of the peripheral (cochlea and auditory nerve) or central auditory nervous systems (Henry 2005). Theories involving the peripheral systems include the discordant damage theory, which predicts that the loss of outer hair cell (OHC) function where inner hair cell (IHC) function is left intact leads to a release from inhibition of IHC and aberrant activity (typically hyperactivity) in the auditory nerve (Jastreboff 1990). Such aberrant auditory nerve activity can also have a biochemical basis, resulting from excitotoxicity or stress-induced enhancement of IHC glutamate release with upregulation of N-methyl-D-aspartate (NMDA) receptors (Guitton 2003; Sahley 2001). In the central auditory system, structures implicated as possible sites of tinnitus generation include the dorsal cochlear nucleus (Middleton 2011; Pilati 2012), the inferior colliculus (Dong 2010; Mulders 2010), and the auditory and non-auditory cortex (discussed further below). There is a strong rationale to say that it is a direct consequence of maladaptive neuroplastic responses to hearing loss (Møller 2000; Mühlnickel 1998). This process is triggered by sensory deafferentation and a release from lateral inhibition in the central auditory system allowing irregular spontaneous hyperactivity within the central neuronal networks involved in sound processing (Eggermont 2004; Rauschecker 1999; Seki 2003). As a consequence of this hyperactivity, a further physiological change noted in tinnitus patients is an increased spontaneous synchronous activity occurring at the cortical level, measurable using electroencephalography (EEG) or magnetoencephalography (MEG) (Dietrich 2001; Tass 2012; Weisz 2005).

Another physiological change thought to be involved in tinnitus generation is a process of functional reorganisation, which amounts to a change in the response properties of neurons within the primary auditory cortex to external sounds. This effect is well demonstrated physiologically in animal models of hearing loss (Engineer 2011; Noreña 2005). Evidence in humans, however, is limited to behavioural evidence of cortical reorganisation after hearing loss demonstrating improved frequency discrimination ability at the audiometric edge (Kluk 2006; McDermott 1998; Moore 2009; Thai-Van 2002; Thai-Van 2003), although Buss 1998 did not find this effect. For comprehensive reviews of these physiological models, see Adjamian 2009 and Noreña 2011. It is also proposed that spontaneous hyperactivity could cause an increase in sensitivity or 'gain' at the level of the cortex, whereby neural sensitivity adapts to the reduced sensory inputs, in effect stabilising mean firing and neural coding efficiency (Noreña 2011; Schaette 2006; Schaette 2011). However, such adaptive changes would be achieved at the cost of amplifying 'neural noise' due to the overall increase in sensitivity, ultimately resulting in the generation of tinnitus.

Increasingly, non-auditory areas of the brain, particularly areas associated with emotional processing, are also implicated in the maintenance of bothersome tinnitus (Rauschecker 2010; Vanneste 2012). Vanneste 2012 recently described tinnitus as "an emergent property of multiple parallel dynamically changing and partially overlapping sub-networks", implicating the involvement of many structures of the brain more associated with memory and emotional processing in tinnitus generation. Identification of the structural components of individual neural networks responsible for either tinnitus generation or tinnitus intrusiveness, which are independent of those for hearing loss, remains open to future research, however (Melcher 2013). One further complication in understanding the pathophysiology of tinnitus is that not all people with hearing loss have tinnitus, and not all people with tinnitus have a clinically significant hearing loss. There are possible explanations for this, however. For example, König 2006 found that the maximum slope within audiograms was higher in people with tinnitus than in people with hearing loss who do not have tinnitus, despite their 'non-tinnitus' group having the greater mean hear-

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ing loss. This suggests that a contrast in sensory inputs between regions of normal and elevated threshold may be more likely to result in tinnitus.

Description of the intervention

Glutamate is the main excitatory neurotransmitter in the hearing brain. The agonistic mechanism of action of glutamate in the central nervous system is mostly mediated by ionotropic receptors (iGluR), namely N-methyl-D-aspartate (NMDA) (Kornhuber 1999) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and metabotropic receptors (mGluR) (Akirav 2007; Myers 2011; Zushida 2007). Both NMDA and AMPA receptors have been associated with the spontaneous and sound-induced depolarisation patterns of the hearing brain (Ehrenberger 1995; Kelly 2000). In the cochlea, only mGluR have been identified (Ehrenberger 1995).

Several neurodegenerative diseases, such as Huntington's, Parkinson's and Alzheimer's disease, are associated with chronic malfunctioning of the glutamate systems in the brain. Its overproduction in the central nervous system has toxic effects (Eggermont 2004), whereby the over-activation of glutamate receptors leads to neuronal cell death (Choi 1990). Blocking glutamate receptors with glutamate receptor antagonists therefore has protective effects (Udilova 2003) against high levels of glutamate (Clifford 1990; Lancelot 1998; Sperk 1994), and they have been used therapeutically for a number of conditions (Elgoyhen 2010). For tinnitus, it has been hypothesised that the excessive release of glutamate between the inner hair cell and the terminal fibres of the auditory nerve at the synaptic cleft, as a result of noise exposure, for example, may generate tinnitus (Figueiredo 2008). Excess glutamate may lead to increased expression of glutamate receptors, making cells increasingly sensitive to the excitatory neurotransmitter, resulting ultimately in excitotoxicity. Glutamate receptor antagonists therefore are a theoretically logical approach to breaking this 'cycle'. The intended main purpose of glutamate receptor antagonists is to reduce tinnitus-related activity in the brain and thereby reduce symptom severity. This may be evidenced by a reduction in or extinction of tinnitus-related distress, anxiety or insomnia. To date, a number of drugs with glutamate receptor antagonist properties, including acamprosate, caroverine, memantine and flupirtine, have been indicated for tinnitus (Azevedo 2007; Denk 1997; Ehrenberger 2005; Salembier 2006). Depending on the drug, the possible adverse effects include gastrointestinal upset (diarrhoea, gastric colic or nausea (Quint 2002; Sass 1996); dry mouth and pruritus (Herrmann 1986); and central nervous system (CNS) effects including hallucinations, lightheadedness, dizziness, fatigue, headache, out-of-body sensation, nightmares and sensory changes (Chizh 2005; Herrmann 1986; Sass 1996). Drug intolerance is frequently associated with hallucination or dissociative mental state (Chizh 2005).

Additional GluR antagonists may be identified during the searches for this review and we will also consider these.

How the intervention might work

When inner hair cells are damaged, for example by noise exposure, ototoxic drugs or as a result of disease, there is an excess production of glutamate, and hyperactivation and over-expression of NMDA glutamate receptors in the cochlea resulting in excitotoxicity (Pujol 1993). This triggers excessive entry of calcium into the primary auditory neurons, with subsequent osmotic swelling and cell lysis. Glutamate receptor antagonists and agonists of GABA receptors decrease excitatory glutamatergic activity, enhance inhibitory GABAergic activity in the auditory pathways and attenuate the influx of calcium. Glutamate receptor antagonists could therefore be useful for treating tinnitus.

Why it is important to do this review

At present, there is no standard treatment modality for tinnitus. In fact, current practice guidelines recommend against the routine use of any medications such as antidepressants or anxiolytics for tinnitus (Tunkel 2014). A drug that affects change in tinnitus-generating neural activity is needed.

The finding of excitotoxic effects in the auditory pathways has increased attention on the potential for treating tinnitus by blocking glutamate binding sites (Puel 1998). Glutamate receptor antagonists are therefore a potentially useful and logical approach to drug therapy for tinnitus, but they have not been subjected to a systematic review as a drug class in their own right. Furthermore there are sub-analyses and meta-analyses that need to be conducted to provide an authoritative review in the field.

Ultimately, a drug treatment for tinnitus is desirable. This review will support the field of drug development and drug trials in tinnitus.

OBJECTIVES

To evaluate the effects and safety of glutamate receptor antagonist medications prescribed for tinnitus.

METHODS

Criteria for considering studies for this review

Types of studies

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Randomised, quasi-randomised or cross-over controlled trials.

Types of participants

Inclusion criteria

Participants of any age presenting with subjective self-reported tinnitus of any duration (less than six months/six months or more).

Exclusion criteria

- Objective tinnitus
- Conductive or mixed type hearing loss
- Middle ear disorders
- Temporomandibular joint disorders
- Tumour in origin
- Previous mastoid surgery

Types of interventions

We will include studies using any dosage or route of administration of glutamate receptor antagonists.
Comparators are:

- placebo;
- no treatment (receiving neither placebo nor any alternative treatments);
- alternative therapies (hearing aids, sound generators, tinnitus retraining therapy (TRT) (these will be pooled in meta-analyses), cognitive behavioural therapy (CBT), counselling, education/information only (these will be pooled in meta-analyses)).

Co-intervention will be allowed if given to both study arms such that any difference in effects can be considered to be due to the drug component of treatment.
The main possible comparison pair is:

- glutamate receptor antagonists *versus* placebo.

Other possible comparison pairs are:

- glutamate receptor antagonists *versus* no treatment;
- glutamate receptor antagonists *versus* sound therapy (hearing aids, sound generators, TRT);
- glutamate receptor antagonists *versus* psychotherapy (CBT, counselling, education/information only).

Types of outcome measures

We will analyse these outcomes in the review, but they will not be used as a basis for including or excluding studies.
We will measure short-term outcomes at any time point less than four weeks and we will measure long-term outcomes at any time point after four weeks.

Primary outcomes

- Tinnitus-specific health-related quality of life, measured as the global score on a validated multi-item tinnitus questionnaire, such as those listed in Table 1.
- Significant adverse effect: hallucination or dissociative mental state.

Secondary outcomes

- Health-related quality of life, as measured with validated multi-item questionnaires, such as the HUI-3, EQ-5D or SF-36.
- Generalised anxiety, as measured by validated multi-item questionnaires, such as the Hospital Anxiety and Depression Scale (HADS) or Beck Anxiety Inventory (BAI).
- Generalised depression, as measured by validated multi-item questionnaires, such as the Hospital Anxiety and Depression Scale (HADS) or Beck Depression Inventory (BDI).
- Other adverse effects (the expected adverse effects are headache and gastrointestinal effects).

We will aim to measure acute responses at two weeks and long-term responses at three months.

Search methods for identification of studies

The Cochrane ENT Information Specialist will conduct systematic searches for randomised controlled trials and controlled clinical trials. There will be no language, publication year or publication status restrictions. We may contact original authors for clarification and further data if trial reports are unclear and we will arrange translations of papers where necessary.

Electronic searches

Published, unpublished and ongoing studies will be identified by searching the following databases from their inception:

- Cochrane Register of Studies Online (search to date);
- PubMed (1946 to date);
- Ovid EMBASE (1974 to date);
- EBSCO CINAHL (1982 to date);
- Ovid CAB abstracts (1910 to date);
- LILACS (search to date);
- KoreaMed (search to date);
- IndMed (search to date);
- PakMediNet (search to date);
- Web of Knowledge, Web of Science (1945 to date);
- CNKI (searched via Google Scholar to date);
- ClinicalTrials.gov, www.clinicaltrials.gov (search via the Cochrane Register of Studies to date);
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), www.who.int/ictrp (search to date);

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- ISRCTN, www.isrctn.com (search to date);
- Google Scholar, scholar.google.co.uk (search to date);
- Google, www.google.com (search to date).

The subject strategies for databases will be modelled on the search strategy designed for CENTRAL (Appendix 1). Where appropriate, these will be combined with subject strategy adaptations of the highly sensitive search strategy designed by Cochrane for identifying randomised controlled trials and controlled clinical trials (as described in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0, Box 6.4.b. (Handbook 2011)).

Searching other resources

We will scan the reference lists of identified publications for additional trials and contact trial authors if necessary. In addition, the Information Specialist will search PubMed, TRIPdatabase, *The Cochrane Library* and Google to retrieve existing systematic reviews relevant to this systematic review, so that we can scan their reference lists for additional trials. We will search for conference abstracts using the Cochrane ENT Trials Register and EMBASE.

Data collection and analysis

Selection of studies

Two review authors (IT, PW) will independently perform study selection based on predetermined eligibility criteria. After the duplicates from the search have been removed, we will screen the titles and abstracts. We will obtain and screen the full texts of selected studies. We will resolve any disagreements over study selection by consensus after discussion. The third author (SA) will adjudicate if necessary.

Data extraction and management

Two review authors (IT, PW) will collect data independently according to the recommendations of the*Cochrane Handbook for Systematic Reviews of Interventions* and enter data onto a predetermined data collection spreadsheet. We will use a standard form created for this review to extract the following information from each included study:

- Study design (RCT/quasi-RCT/cluster-RCT; parallel/crossover)
- Unit of randomisation
- Unit of analysis
- Setting
- Inclusion criteria for the study
- Exclusion criteria for the study
- Age
- Gender
- Duration of tinnitus symptoms (acute versus chronic)
- Glutamate receptor antagonist agent
- Dosage
- Route of administration
- Type of comparator
- Duration of intervention
- Duration of follow-up
- Details of co-interventions
- The number of participants in each arm
- Baseline, post-intervention and follow-up questionnaire scores and results of statistical analysis
- Adverse events
- Amount of missing data
- Sources of funding

We will resolve any disagreements over data by using the adjudication of the third author (KS) if necessary.
We will approach study authors for unpublished information that is missing from reports of the included studies and any additional information required for completion of the data extraction.

Assessment of risk of bias in included studies

IT and SA will undertake assessment of the risk of bias of the included trials independently, with the following taken into consideration, as guided by the*Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011):

- sequence generation;
- allocation concealment;
- blinding;
- incomplete outcome data;
- selective outcome reporting; and
- other sources of bias.

We will use the Cochrane 'Risk of bias' tool in RevMan 5.3 (RevMan 2014), which involves describing each of these domains as reported in the trial and then assigning a judgement about the adequacy of each entry: 'low', 'high' or 'unclear' risk of bias. We will define overall high risk of bias as having a high risk of bias for at least one of blinding, incomplete outcome data or selective outcome reporting.

Measures of treatment effect

We will assess improvement in tinnitus and quality of life using the mean difference (MD) with 95% confidence interval (CI) if the outcomes are measured in the same way. If not, we will use the standardised mean difference (SMD). Change scores will be preferred. However, final values can be used when there is no difference between groups in baseline values. For adverse effects of glutamate receptor antagonists, we will calculate the risk ratio (RR) with 95% CI.

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Unit of analysis issues

For parallel-group RCTs the unit of analysis will be the group mean. We will analyse cluster-randomised trials based on the level of allocation, i.e. clusters of patients. For cross-over trials we will only include data from the first period (i.e. pre-cross-over). For multi-arm trials, we will select any comparisons defined in the protocol where data from two arms (glutamate receptor antagonists versus comparator) are collected at the same time.

Dealing with missing data

We will contact corresponding authors by email to request missing study details and data. We will base the analyses on intention-to-treat. We will impute the missing data with replacement values and treated them as if they were observed. For continuous outcomes, the last observation will be carried forward. For adverse events, we will carry out an available case analysis. For other dichotomous outcomes (not adverse events), we will apply the assumption that all patients with missing data do not have an event. For missing standard deviations, we will use either 95% confidence intervals (CIs), interquartile ranges or standard errors for estimation to impute standard deviations.

Assessment of heterogeneity

We will assess the heterogeneity between studies by inspecting forest plots and using the Chi^2 test with an alpha of 0.05 and the I^2 statistic (Handbook 2011). If confidence intervals for the results of individual studies have poor overlap, this generally indicates the presence of heterogeneity. I^2 values of 25%, 50% and 75% correspond to low, medium and high levels of heterogeneity, respectively.

Assessment of reporting biases

We will create a funnel plot to assess the potential for publication bias if we can include at least 10 studies in the meta-analyses.

Data synthesis

We will use RevMan 5.3 to carry out the meta-analyses for comparable trials and outcomes. We will pool data using a fixed-effect model if there is no heterogeneity among studies. We will use a random-effects model if heterogeneity cannot be ruled out. We will only pool data from different questionnaires where there is evidence of good convergent validity.

We will stratify studies into four comparisons:

- glutamate receptor antagonists versus placebo;
- glutamate receptor antagonists versus no treatment;
- glutamate receptor antagonists versus sound therapy (hearing aids, sound generators, TRT);
- glutamate receptor antagonists versus psychotherapy (CBT, counselling, education/information only).

We will initially combine studies with any dosage, any route and any duration of treatment. We will pool data from two arms that are of interest (as per comparison) from studies with multiple arms. We will present different types of data as per outcomes. We will present dichotomous data as a risk ratio with its 95% confidence interval. We will present continuous data as the mean difference (MD) with 95% confidence interval (CI) if the outcomes are measured in the same way. If not, we will present them as the standardised mean difference (SMD).

Subgroup analysis and investigation of heterogeneity

Where heterogeneity is identified we will explore the following possible sources: duration of tinnitus, dose of drug, method of administration and comparator.

- Duration: whether tinnitus is acute (less than six months since onset) or chronic (six months or more since onset).
- Dosage: half of the usual dose, the usual dose and a double dose of glutamate receptor antagonists have been studied for the treatment of tinnitus. We will therefore perform subgroup analysis with three subgroups: 'low dose' versus 'usual dose' versus 'high dose'.
    - Acamprosate: less than 666 mg versus 666 mg versus greater than 666 mg three times per day.
    - Caroverine: less than 40 mg versus 40 mg to 80 mg versus greater than 80 mg daily.
    - Memantine: less than 5 mg versus 5 mg to 90 mg versus greater than 90 daily.
    - Flupirtine: less than 100 mg versus 100 mg to 200mg versus greater than 200 mg three times per day.
- Method of administration: subgroup analyses will compare the effects of oral, intravenous or topical administration.
- Different types of comparator using alternative treatment.

Sensitivity analysis

We will perform sensitivity analysis to explore the robustness of our assumptions from the data. We will perform sensitivity analysis to test whether study risk of bias affects the data by excluding studies with high risk of bias from the meta-analyses and assessing any difference in the overall results. We will define overall high risk of bias as having a high risk of bias for at least one of blinding, incomplete outcome data or selective outcome reporting.

GRADE and 'Summary of findings'

At least two independent authors will use the GRADE approach to assess the overall quality of evidence. The quality of evidence reflects the extent to which we are confident that an estimate of effect is correct and we will apply this in the interpretation of results. There are four possible ratings: high, moderate, low and very low. A rating of high quality of evidence implies that we are confident in our estimate of effect and that further research is very

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unlikely to change our confidence in the estimate of effect. A rating of very low quality implies that any estimate of effect obtained is very uncertain.

The GRADE approach rates evidence from RCTs that do not have serious limitations as high quality. However, several factors can lead to the downgrading of the evidence to moderate, low or very low. The degree of downgrading is determined by the seriousness of these factors:

- study limitations (risk of bias);
- inconsistency;
- indirectness of evidence;
- imprecision; and
- publication bias.

We will include a 'Summary of findings' table, constructed according to the recommendations described in Chapter 11 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011). The outcomes that we will present in the 'Summary of findings' table are: tinnitus-specific and health-related quality of life, generalised anxiety and depression, and adverse events.

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* *Indicates the major publication for the study*

ADDITIONAL TABLES

Table 1. Tinnitus questionnaires

Questionnaire (author, year)	Number of items and subscales	Psychometric properties
Tinnitus Handicap Inventory (Newman 1996)	25 items, 3 subscales	a = 0.93 for total scale
Tinnitus Functional Index (Meikle 2012)	25 items, 8 subscales	a = 0.97 for total scale
Tinnitus Handicap Questionnaire (Kuk 1990)	27 items, 3 subscales	a = 0.93 for total scale
Tinnitus Questionnaire (Hallam 1996)	52 items, 5 subscales	a = 0.91 for total scale; for subscales a = 0.76 to a = 0.94
Tinnitus Reaction Questionnaire (Wilson 1991)	26 items, 4 subscales	a = 0.96 and a test-retest correlation of r = 0.88
Tinnitus Severity Scale (Sweetow 1990)	15 items	Not reported

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APPENDICES

Appendix 1. CRS Online and PubMed search strategy

CRS Online	PubMed
#1 MESH DESCRIPTOR Tinnitus EXPLODE ALL TREES #2 tinnit*:TI,AB,KY #3 #1 OR #2 #4 MESH DESCRIPTOR Receptors, Glutamate EXPLODE ALL TREES #5 MESH DESCRIPTOR Glutamates EXPLODE ALL TREES #6 MESH DESCRIPTOR Excitatory Amino Acid Antagonists EXPLODE ALL TREES #7 MESH DESCRIPTOR Receptors, N-Methyl-D-Aspartate EXPLODE ALL TREES #8 MESH DESCRIPTOR GABA Agents EXPLODE ALL TREES #9 MESH DESCRIPTOR Alcohol Deterrents EXPLODE ALL TREES #10 MESH DESCRIPTOR Calcium Channel Blockers EXPLODE ALL TREES #11 MESH DESCRIPTOR Calcium Channel Agonists EXPLODE ALL TREES #12 MESH DESCRIPTOR Quinoxalines EXPLODE ALL TREES #13 (glutamate* or glumatic* or antiglutamat*):TI,AB,KY #14 (GABA or GABAergic or AMPA or NMDA or AOAA):TI,AB,KY #15 (aptiganel or caroverin* or conantokin or conotoxin or Dextromethorphan or Dizocilpine or eliprodil or gabapentin or gacyclidine or Ibogaine or ifenprodil or Ketamin* or ketobemidone or Kynurenic or lamotrigine or licostinel or Memantin* or Phencyclidine or Phenobarbital or Riluzole or selfotel):TI,AB,KY #16 (Adipiplon or Allylglycine or Alprazolam or Aminooxyacetic or Amobarbital or "arbaclofen placarbil" or Baclofen or Barbital or Bicuculline or "bicuculline methochloride" or Bromazepam or Chlordiazepoxide or Chlormethiazole or Clonazepam or "Clorazepate Dipotassium" or Clozapine or Diazepam or Estazolam or Flumazenil or Flunitrazepam or Flurazepam or gabazine or gaboxadol or Hexobarbital or imidazenil or indiplon or isoguvacine or lesogaberan or Lorazepam or Medazepam or Mephobarbital or Midazolam or Muscimol or nimetazepam or Nitrazepam or Nordazepam or Oxazepam or Pentobarbital or Pentylenetetrazole or phaclofen or phenazepam or Phenobarbital or phetharbital or Picrotoxin or picrotoxinin or peperidine or Prazepam or progabide or saclofen or Secobarbital or Temazepam or Thiamylal or Thiopental or tiagabine or tramiprosate or Triazolam or valproic or Vigabatrin or zaleplon or Zolazepam or zolpidem):TI,AB,KY	#1 "Tinnitus"[Mesh] #2 tinnit*[Title/Abstract] #3 (#1 OR #2) #4 "Glutamates"[Mesh] #5 "Receptors, Glutamate"[Mesh] #6 (("Excitatory Amino Acid Antagonists" [Pharmacological Action] OR "Excitatory Amino Acid Antagonists"[Mesh])) #7 (("Receptors, N-Methyl-D-Aspartate/antagonists and inhibitors"[Mesh])) #8 (("GABA Agents" [Pharmacological Action] OR "GABA Agents"[Mesh])) #9 (("Alcohol Deterrents" [Pharmacological Action] OR "Alcohol Deterrents"[Mesh])) #10 (("Calcium Channel Blockers" [Pharmacological Action] OR "Calcium Channel Blockers"[Mesh])) #11 "Calcium Channel Agonists"[Mesh] #12 "Quinoxalines"[Mesh] #13 (glutamate*[Title/Abstract] OR glumatic*[Title/Abstract] OR antiglutamat*[Title/Abstract]) #14 (GABA[Title/Abstract] OR GABAergic[Title/Abstract] OR AMPA[Title/Abstract] OR NMDA[Title/Abstract] OR AOAA[Title/Abstract]) #15 (aptiganel[Title/Abstract] OR caroverin*[Title/Abstract] OR conantokin[Title/Abstract] OR conotoxin[Title/Abstract] OR Dextromethorphan [Title/Abstract] OR Dizocilpine[Title/Abstract] OR eliprodil[Title/Abstract] OR gabapentin[Title/Abstract] OR gacyclidine[Title/Abstract] OR Ibogaine[Title/Abstract] OR ifenprodil[Title/Abstract] OR Ketamin*[Title/Abstract] OR ketobemidone[Title/Abstract] OR Kynurenic[Title/Abstract] OR lamotrigine[Title/Abstract] OR licostinel[Title/Abstract] OR Memantin*[Title/Abstract] OR Phencyclidine[Title/Abstract] OR Phenobarbital[Title/Abstract] OR Riluzole[Title/Abstract] OR selfotel[Title/Abstract]) #16 (acamprosate[Title/Abstract] OR daidzin[Title/Abstract] OR Disulfiram[Title/Abstract] OR metadoxine[Title/Abstract]) #17 (Adipiplon[Title/Abstract] OR Allylglycine[Title/Abstract] OR Alprazolam[Title/Abstract] OR Aminooxyacetic[Title/Abstract] OR Amobarbital[Title/Abstract] OR "arbaclofen placarbil"[Title/Abstract] OR Baclofen[Title/Abstract] OR Barbital[Title/Abstract] OR Bicuculline[Title/Abstract] OR "bicuculline methochloride"[Title/Abstract] OR Bromazepam[Title/Abstract] OR Chlordiazepoxide[Title/Abstract] OR Chlormethi-

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(*Continued*)

#17 (acamprosate or daidzin or Disulfiram or metadoxine):TI,AB,KY
#18 (Amlodipine or Amrinone or anandamide or anipamil or azimilide or Bencyclane or benidipine or Bepridil or berbamine or canadine or carboxyamido or caroverin* or cilnidipine or Cinnarizine or clentiazem or clevidipine or Conotoxins or "Conus magus toxin" or darodipine or dauricine or devapamil or Diltiazem or dotarizine or efonidipine or emopamil or gabapentin or Gallopamil or enpiperate or eperisone or falipamil or fantofarone or fasudil or Felodipine or fenamic acid or Fendiline or Flunarizine or fosfedil or Isradipine or lacidipine or lamotrigine or lercanidipine or Lidoflazine or lomerizine or Magnesium or manidipine or manoalide or mepirodipine or Mibefradil or monatepil or naftopidil or Nicardipine or Nifedipine or niguldipine or niludipin or nilvadipine or Nimodipine or Nisoldipine or Nitrendipine or norverapamil or ochratoxin OR octylonium or Agatoxin or Conotoxin or osthol or oxodipine or Perhexiline or pinaverium or piperidine or pranidipine or pregabalin or Prenylamine or risedronic or ryodipine or sesamodil or stepholidine or temiverine or terodiline or tetrahydropalmatine or tetrandrine or Tiapamil or tolfenamic or tranilast or Verapamil or ziconotide):TI,AB,KY
#19 (AP5 or APV or DXM or DXO or MK-801 or Endabuse or Vadilex or INN or Ketalar or ketaset or ketanest or calipsol or kalipsol or calypsol or KYNA or KYN or USAN or fycompa or PCP or "Angel dust" or Fenciclidina or Phencyclidinum or Baclofen or Aminalon* or Gammalon or Neramexane or Flupirtine or serynyl or serylan or spadon or axura or akatinol or abixa or memox or phosphonovaleric or phosphonopentanoate or Methylmorphinan or Methoxyibogamine or Namenda or Ebixa or Axura or aminoadamantane or dimethyladamantane or acetylhomotaurine or AOTA campral or zule):TI,AB,KY
#20 (gamma and Aminobutyric):TI,AB,KY
#21 (calcium and block*):TI,AB,KY
#22 ((amino* or oxyacetic or Aminobutyric) and acid*):TI,AB,KY
#23 ((neurotransmi* or excitato*) and antagonist*):TI,AB,KY
#24 #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23
#25 #3 AND #24

azole[Title/Abstract] OR Clonazepam[Title/Abstract] OR "Clorazepate Dipotassium"[Title/Abstract] OR Clozapine[Title/Abstract] OR Diazepam[Title/Abstract] OR Estazolam[Title/Abstract] OR Flumazenil[Title/Abstract] OR Flunitrazepam[Title/Abstract] OR Flurazepam[Title/Abstract] OR gabazine[Title/Abstract] OR gaboxadol[Title/Abstract] OR Hexobarbital[Title/Abstract] OR imidazenil[Title/Abstract] OR indiplon[Title/Abstract] OR isoguvacine[Title/Abstract] OR lesogaberan[Title/Abstract] OR Lorazepam[Title/Abstract] OR Medazepam[Title/Abstract] OR Mephobarbital[Title/Abstract] OR Midazolam[Title/Abstract] OR Muscimol[Title/Abstract] OR nimetazepam[Title/Abstract] OR Nitrazepam[Title/Abstract] OR Nordazepam[Title/Abstract] OR Oxazepam[Title/Abstract] OR Pentobarbital[Title/Abstract] OR Pentylenetetrazole[Title/Abstract] OR phaclofen[Title/Abstract] OR phenazepam[Title/Abstract] OR Phenobarbital[Title/Abstract] OR phetharbital[Title/Abstract] OR Picrotoxin[Title/Abstract] OR picrotoxinin[Title/Abstract] OR peperidine[Title/Abstract] OR Prazepam[Title/Abstract] OR progabide[Title/Abstract] OR saclofen[Title/Abstract] OR Secobarbital[Title/Abstract] OR Temazepam[Title/Abstract] OR Thiamylal[Title/Abstract] OR Thiopental[Title/Abstract] OR tiagabine[Title/Abstract] OR tramiprosate[Title/Abstract] OR Triazolam[Title/Abstract] OR valproic[Title/Abstract] OR Vigabatrin[Title/Abstract] OR zaleplon[Title/Abstract] OR Zolazepam[Title/Abstract] OR zolpidem[Title/Abstract])
#18 (AP5[Title/Abstract] OR APV[Title/Abstract] OR DXM[Title/Abstract] OR DXO[Title/Abstract] OR MK-801[Title/Abstract] OR Endabuse[Title/Abstract] OR Vadilex[Title/Abstract] OR INN[Title/Abstract] OR Ketalar[Title/Abstract] OR ketaset[Title/Abstract] OR ketanest[Title/Abstract] OR calipsol[Title/Abstract] OR kalipsol[Title/Abstract] OR calypsol[Title/Abstract] OR KYNA[Title/Abstract] OR KYN[Title/Abstract] OR USAN[Title/Abstract] OR fycompa[Title/Abstract] OR PCP[Title/Abstract] OR "Angel dust"[Title/Abstract] OR Fenciclidina[Title/Abstract] OR Phencyclidinum[Title/Abstract] OR Baclofen[Title/Abstract] OR Aminalon*[Title/Abstract] OR Gammalon[Title/Abstract] OR Neramexane[Title/Abstract] OR Flupirtine[Title/Abstract] OR serynyl[Title/Abstract] OR serylan[Title/Abstract] OR spadon[Title/Abstract] OR axura[Title/Abstract] OR akatinol[Title/Abstract] OR abixa[Title/Abstract] OR memox[Title/Abstract] OR phosphonovaleric[Title/Abstract] OR phosphonopentanoate[Title/Abstract] OR Methylmorphinan[Title/Abstract] OR Methoxyibogamine[Title/Abstract] OR Namenda[Title/Abstract] OR Ebixa[Title/Abstract] OR Axura[Title/Abstract] OR aminoadamantane[Title/Abstract] OR dimethyladamantane[Title/Abstract] OR acetylhomotaurine[Title/Abstract] OR AOTA campral[Title/Abstract] OR zule[Title/Abstract])

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(*Continued*)

	#19 (gamma[Title/Abstract] AND Aminobutyric[Title/Abstract]) #20 (calcium[Title/Abstract] AND block*[Title/Abstract]) #21 ((amino*[Title/Abstract] OR oxyacetic[Title/Abstract] OR Aminobutyric[Title/Abstract])) AND acid*[Title/Abstract] #22 ((neurotransmi*[Title/Abstract] OR excitato*[Title/Abstract])) AND antagonist*[Title/Abstract] #23 (#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #2- OR #21 OR#22) #24 #3 AND #23

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